REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

The rejection of claims 67-76 under the judicially-created doctrine of obviousness-type double patenting for obviousness over claims 1-18 of U.S. Patent No. 6,252,130 is respectfully traversed in view of applicant's submission of the accompanying terminal disclaimer.

The rejection of claims 67-76 under 35 U.S.C § 112(1st para.) for lack of enablement is respectfully traversed.

It is the position of the U.S. Patent and Trademark Office ("PTO") that the specification of the present invention does not enable one of ordinary skill in the art to make and use the present invention in a manner commensurate with the scope of the claims.

One basis for the rejection is that, according to the PTO, embryonic stem ("ES") cells from mammals were not available on the November 13, 1995, filing date of grandparent U.S. Provisional Patent Application Serial No. 60/006,622. Applicants respectfully disagree. Travis et al. "Monkeying Around With Stem Cells," *Science* 148:139 (August 26, 1995) (attached hereto as Appendix 1) and Thomson et al., "Isolation of a Primate Embryonic Stem Cell Line," *Proc. Nat'l. Acad. Sci. USA* 92:7844-48 (1995) ("Thomson") (attached hereto as Appendix 2) show that monkey embryonic stem cells were available before November 13, 1995. Wheeler, "Development and Validation of Swine Embryonic Stem Cells: A Review" Reprod. Fertil. Dev. 6:563-68 (1994) ("Wheeler") (attached hereto as Appendix 3) shows that swine ES cells were available and had been demonstrated to be capable of producing chimeric swine as of 1994. First, et. al., "Systems for Production of Calves from Cultured Bovine Embryonic Cells," Reprod. Fertil. Dev. 6: 553-62 (1994) ("First") (attached hereto at Appendix 4) describes the production of calves from cultured bovine embryonic stem cells. In addition, the ES cells from all of the following species had been isolated by the November 1995 filing date: hamster (Doetschman, et. al., "Establishment of Hamster Blastocyst-Derived Embryonic Stem (ES) Cells," Devel. Biol. 127: 224-27 (1988)(attached hereto at Appendix 5)); rabbit (Graves, et. al., "Derivation and Characterization of Putative Pluripotent Embryonic Stem Cells From Preimplantation Rabbit Embryos" Molec. Reprod. & Develop. 36: 424-33 (1993)(attached hereto at Appendix 6)); rat (Lannaccone, et. al., "Pluripotent Embryonic Stem Cells from the Rat are Capable of Producing Chimeras," Develop. Biol. 163: 288-92 (1994)(attached hereto

at Appendix 7)); Sukoyan, et. al., "Isolation and Cultivation of Blastocyst-Derived Stem Cell Lines from American Mink (*Mustela vison*)," Molec. Reprod. & Develop. 33: 418-31 (1992)(attached hereto at Appendix 8)); sheep (Piedrahita, et. al., "On the Isolation of Embryonic Stem Cells: Comparative Behavior of Murine, Porcine, and Ovine Embryos," Theriogen. 34(5): 879-901 (1990)(attached hereto at Appendix 9)); and humans (Bongso, et. al., "Isolation and Culture of Inner Cells Mass Cells from Human Blastocyts," Human Reprod. 9(11): 2110-17 (1994)(attached hereto at Appendix 10)). Thus, the alleged unavailability of mammalian embryonic stem cells in 1995 is inaccurate and can form no basis for rejecting the claims under 35 U.S.C. § 112 (1st para.).

Another basis for the nonenablement rejection is that the totipotency of the chimeric, non-murine embryonic stem was not established as of the effective filing date of the present application. However, the outstanding office acknowledges that totipotent murine embryonic stem cells existed at that time. Further, as indicated by First and Wheeler, totipotency of embryonic stem cells in swine and cows had been demonstrated by that time. Thus, a lack of enablement rejection cannot be properly based on an inability to produce totipotent embryonic stem cells from mammals.

To satisfy the enablement requirement under 35 U.S.C. § 112 (1st para.), the specification of a patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'. *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 42 USPQ2d 1001 (Fed. Cir. 1997). It is well settled that enablement can be established with evidence in post-filing date publications showing that the various techniques taught in the application were successful. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.2d 1313, 65 USC2d 1385 (2003).

The disclosure of the present application shows that transgenic mice can be produced by microinjection of the subject combinatorial substrate into the pronuclei of fertilized eggs which are transferred into the oviduct of pseudopregnant females (see Example 4). The resulting mice were then shown to be able to promote *in vivo* recombination as a result of somatic delivery of recombinase (Example 5). As an alternative to microinjection, the present application teaches that transgenic animals can be produced by transfection of embryonal stem cells (page 16, lines 5-7). The PTO acknowledges that at the time the grandparent application was filed, those of ordinary skill in the art recognized that murine embryonal stem cells were totipotent and, therefore, could be used to produce transgenic mice in accordance with the present invention. Thus, the only issue is whether one

of ordinary skill in the art would have been able to produce other transgenic mammals by transfection of embryonal stem cells from such other mammals.

The literature shows that those skilled in the art would clearly answer this question in the affirmative. At the time the grandparent application was filed, totipotent embryonic stem cells in mice, cows, and pigs were known. Thus, in these species, one of ordinary skill in the art would have expected to produce transgenic animals in accordance with the present application. Moreover, given the success achieved with mice, cows, and pigs prior to the effective filing date of the present application, one or ordinary skill in the art would have every reason to expect that the present invention could be carried out in other species.

The PTO relies on the statement on p. 1351 of Wheeler, et. al., "Transgenic Technology and Applications in Swine," Therlogen. 56: 1345-69 (2001)("Wheeler") that "[f]urthermore, validation of the totipotency of these embryo-derived ES cell lines awaits confirmation." However, this provides no support for a non-enablement rejection. The fact that embryonal stem cells other than those from mice had not been tested for totipotency does not mean that they would not work in accordance with the present invention. As noted above, applicant has shown that the present invention works with mice using microinjection and there is no apparent dispute that it would likewise work by transfection of embryonal stem cells in mice. One of ordinary skill in the art would have expected this technique to work with embryonal stem cells from other species, particularly given the totipotency of embryonic stem cells from pigs and cows. Moreover, as noted by the following statement in Brivanlou, et. al, "Stem Cells—Setting Standards for Human Embryonic Stem Cells", Science 300: 913-16 (2003)(attached hereto as Appendix 11)("Brivanlou"), mouse and human embryonal stem cells share many characteristics:

> As with mouse embryonic stem cells (MESCs), [human embryonic stem cells (HESCs)] exhibit the following basic characteristics: (i) The cells are karyotypically normal, (ii) they survive and proliferate in vitro indefinitely under well-defined tissue culture conditions, (iii) most of the cells recover after freezing and thawing, and (iv) they differentiate into a variety of cell types in vitro and in vivo. (citations omitted)

Id. at 913. Moreover, the art recognizes that HESCs, like MESCs, can be genetically altered. In particular, Brivanlou states:

> A number of reports have documented successful transfection and subsequent expression of genes in HESCs. Human retroviral vectors (such as lentiviruses) and biochemical strategies have shown promise for transfecting HESCs. If HESCs are going to be used for therapy, the possibility of random integration of transfected genes cloned into viral vectors should be addressed with care. Loss-of-function experiments by site-specific recombination (knockouts or knockins) routinely performed in MESCs have recently been reported in HESCs, and provide the opportunity to genetically alter HESCs. (citations omitted).

Id. at 915. Since the art demonstrates the existence of totipotent embryonic stems cells from mice, cows, and pigs and that techniques used to transfect murine embryonal stem cells would be expected to work in human embryonal stem cells, there is no basis to assert that the techniques that applicant taught would not have worked in other species. The fact that the claimed techniques were not actually tested in other species at the time the grandparent provisional application was filed is of no moment. What matters is that the art believes the techniques disclosed by the present application were useful in non-murine species. Accordingly, the enablement rejection with regard to the claimed invention cannot be maintained and should instead be withdrawn.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: September 26, 2003

Michael L. Goldman
Registration No. 30,727

NIXON PEABODY LLP
Clinton Square, P.O. Box 31051
Rochester, New York 14603-1051
Telephone: (585) 263-1304
Facsimile: (585) 263-1600

Certificate of Mailing - 37 CFR 1.8(a)	
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450, on the date below.	
9/26/03 Date	Wendy L. Barry